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The persistent challenge of rheumatic fever in the Northern Mariana Islands

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ABSTRACT

Objectives: Acute rheumatic fever (ARF) is a major cause of morbidity and mortality in developing nations. The objective of this study was to determine the disease burden of ARF among the indigenous and non-indigenous populations of the Northern Mariana Islands.
Methods: This was a chart review of all pediatric outpatients seen from 1984 to 2006 with ICD-9 codes corresponding to rheumatic fever or any rheumatic cardiac sequelae. The study was set in the only comprehensive inpatient facility and only public pediatric clinic in the Northern Mariana Islands.
Results: One hundred fifty-eight cases of ARF were identified. Age at diagnosis ranged from 2.9 to 17.1 years (median 10.6 years). Fever and carditis were the most common presenting findings. The average annualized incidence of ARF was 85.8 per 100 000 person-years for those aged 5–14 years. Sixty-six percent of patients with ARF were of Chamorro or Carolinian ancestry, despite comprising only 39% of the total population, with a combined average annualized incidence of ARF of 167 per 100 000 person-years.
Conclusions: This is the first documentation of the incidence of pediatric ARF in the Northern Mariana Islands, delineating the large disease burden in the indigenous and other Pacific Island ethnic groups. Impediments to diagnosis and primary and secondary prevention were identified. The data provide strong support for the need for primary and secondary prevention of ARF.

1. Introduction

Rheumatic heart disease (RHD) is a major cause of morbidity and mortality in the developing world. It is estimated that over 15 million people have RHD worldwide, with 282 000 new cases and 233 000 deaths annually.[1] Numerous reports have shown an increased incidence in people of various ethnic backgrounds, including Pacific Islanders and Australian aboriginals.[2,3] Samoans living in Samoa and Hawaii, have an estimated prevalence of RHD of 77.8 per 1000 and an incidence of acute rheumatic fever (ARF) of 206 per 100 000, respectively.[2,3] It is unclear why these populations have an increased incidence of ARF, but it is thought to result from a combination of host factors, streptococcal strains, environment, and nutrition. We sought to study the incidence of ARF in the Northern Mariana Islands among the indigenous Chamorros and Carolinians and the non-indigenous populations.

2. Materials and methods

The Northern Mariana Islands, a Commonwealth of the USA, are a chain of 15 islands in the Western Pacific that start 50 miles north of Guam and extend over 400 miles further north. The population of nearly 70 000 is comprised of a mix of Pacific Island groups as well as Chinese, Filipino, Japanese, Korean, Nepalese, Bangladeshi, White Americans, and African Americans and is divided among three islands: Saipan, the capital, with 90% of the population and Tinian and Rota with 5% each. The Commonwealth Health Center (CHC), located on Saipan, is the sole provider of comprehensive inpatient healthcare services in the Northern Mariana Islands, the referral center for the other Mariana Islands, and houses the only public pediatric clinic providing care for the indigent population. The CHC provides care to 75% of the pediatric population and 100% of the uninsured population in the Northern Mariana Islands. There are clinics located on Tinian and Rota, but all complicated pediatric cases, such as ARF, are referred to Saipan for further care. The nearest tertiary care centers are 1500 miles to the west in Japan and the Philippines and 3700 miles to the east in Hawaii. The CHC is able to provide primary care and surgical services as well as diagnostic studies such as echocardiography, but patients who require complex surgical procedures and advanced cardiac imaging must be sent to off-island centers for their care.

We performed a retrospective chart review of ARF presentations from 1984 to 2006. Computer-based records were searched for CHC outpatient pediatric visits with an ICD-9 code corresponding to ARF or any rheumatic cardiac sequelae (390.0–398.99)

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from January 1, 1992, when the computer records began, through November 30, 2006. This initial query returned 223 patients, with encounters in the paper charts dating back to 1984. Records were excluded from analysis if the patient was aged over 21 years before 1992 and if a diagnosis of ARF could not be corroborated in the chart (including cases where the chart could not be located).

The data collected from the medical records included date of birth, date of diagnosis, age at diagnosis, sex, ethnicity, presenting Jones criteria, cardiac involvement at diagnosis, and any recurrences of ARF. Diagnostic criteria for ARF included any illness meeting the Jones criteria.[4] Cases that did not fully satisfy the Jones criteria had often been classified as ARF given the problem of underdiagnosis. Carditis was defined as either a new murmur on physical examination and/or valvular thickening noted on echocardiogram, when available. A streptozyme titer of at least 1:100, an antistreptolysin O titer greater than 150 Todd units, or a throat culture positive for group A Streptococcus was considered evidence of streptococcal infection. In accordance with World Health Organization guidelines, a recurrence of ARF was diagnosed in a patient with prior ARF who had a subsequent episode of illness that either met strict Jones criteria[4] or had several minor criteria with evidence of streptococcal infection.[5] Prior ARF is considered a major criterion.[5]

Incidence data were calculated using census data from 1980, 1990, 1995, and 2000.[6] The denominator was all children aged 5–14 years to be comparable with findings from other studies; a constant population was used for each date range (i.e., 6176 children for all calculations from 1990 through 1994). Cases diagnosed at ages outside of this range were excluded from the incidence calculation. The annual average number of cases of ARF diagnosed over each time period (1984–1989, 1990–1994, 1995–1999, and 2000–2006) constituted the numerator.

There were no data available specifically enumerating the 5–14-year-olds for each ethnic group in order to calculate ethnicity-specific incidences of ARF. Therefore, we estimated the incidence for each ethnic group based on their percentage of the total population and calculating a weighted average population of 5–14-year-olds over the study period for each group. This number constituted the denominator. For example, Chamorros constitute 56.7%, 29%, 23.5%, and 21.3% of the total population for 1984–1989, 1990–1994, 1995–1999, and 2000–2006, respectively, giving a weighted average of 2067.7 Chamorros aged 5–14 years for the entire study period. For the numerator, we used the annual average number of cases over 23 years for each ethnic group. So, for Chamorros, there were a total of 62 cases of ARF in those aged 5–14 years, giving an annual average of 2.7 cases over 23 years. There were insufficient census data to perform this calculation for the one case of ARF among native Hawaiians during the study period. Statistical calculations were performed with OpenEpi version 2.2.1.[7]

3. Results

One hundred fifty-eight new, unique cases of ARF were found through the chart review. Recurrent cases of ARF were not counted in this total. Age at diagnosis ranged from 2.9 to 17.1 years, median 10.6 years; 102 patients (64.6%) were male.

Table 1
Presenting findings of acute rheumatic fever in all patients

Finding	*n*	%
Fever	126	80.8
Antibody titer positive	115	72.7
Carditis	86	54.4
Arthritis	80	51.0
Arthralgia	49	31.2
Throat culture positive	27	31.0
Rash	9	5.7
Chorea	8	5.1

A list of presenting findings is shown in Table 1. Fever was the most prevalent finding, followed by carditis. Throat culture was positive in 31% of patients, but was only obtained in 55% of patients. Seventy-two percent of patients had positive serology as defined in the Methods section, but only 79% of patients had either an antistreptolysin O titer or streptozyme checked and documented. Antistreptolysin O titers ranged from 47 to 3791 Todd units; streptozyme titers ranged from 1:100 to 1:800. Ten patients (8%) had antistreptolysin O titers less than 150 Todd units. No patients presented with subcutaneous nodules. Strict Jones criteria[4] were met in 118 (74.7%) patients. Recurrences were documented in 61 (38.6%) patients.

Table 2 shows the average annualized incidence of ARF for all those aged 5–14 years during the periods 1984–1989, 1990–1994, 1995–1999, and 2000–2006. The average annualized incidence of ARF for the entire study period was 85.8 cases per 100 000 person-years. Four children aged younger than 5 years and 11 aged older than 14 years were excluded from the incidence calculations. Incidence rate ratios comparing each time period are shown in Table 2. We extrapolated ARF incidence for each ethnic group using the census data as explained in the Methods section, with results shown in Table 3.

Ninety-five (66.4%) patients diagnosed with ARF were of Chamorro or Carolinian ancestry, who comprised an average of 39.3% of the population during the study period (Table 3). One hundred thirty-four (93.7%) of the ARF patients were of any Pacific ancestry, although Pacific Islanders comprised an average of 47.1% of the total population over the study period. The combined average annualized incidence for the indigenous Chamorro and Carolinian groups was 167 cases per 100 000 person-years (95% confidence interval 135.8–203.2); incidence rate ratios comparing them to the other ethnic groups are shown in Table 3. There were no cases of ARF among the Chinese, Japanese, Korean, Nepalese, Bangladeshi, or African American ethnic groups, who comprised an average of 25.1% of the population during the study period.

Comparing the percentage of patients with evidence of carditis at diagnosis before and after the acquisition of Doppler echocardiographic equipment produced a *z*-score of 1.57.

Data were not available regarding most patients' use of non-steroidal anti-inflammatory drugs (NSAIDs) prior to ARF diagnosis.

Table 2
Incidence per 100 000 person-years and incidence rate ratios of acute rheumatic fever (ARF) among those aged 5–14 years in the Northern Mariana Islands with 95% confidence intervals in parentheses

	1984–1989	1990–1994	1995–1999	2000–2006	1984–2006
Number ARF (annual mean)	1.2	5.4	4.8	12.1	6.2
Population 5–14 years	4339	6176	8219	9797	7243
Incidence ARF 5–14 years	26.9 (11.8, 53.2)	87.4 (58.8, 125.5)	58.4 (38.3, 85.6)	123.9 (99.6, 152.5)	85.8 (72.6, 100.8)
Incidence rate ratio (reference 2000–2006)	0.22 (0.09, 0.45)	0.71 (0.45, 1.08)	0.47 (0.29, 0.73)	-	-

Table 3
Number of cases of acute rheumatic fever (ARF) and incidence per 100 000 person-years for those aged 5–14 years for the 23-year study period (1984–2006) among the different ethnic groups in the Northern Mariana Islands and population breakdown for the Northern Mariana Islands

Ethnicity	*n*	% of ARF	% of population	Incidence of ARF	Incidence rate ratio (reference indigenous population)[b]
Chamorro[a]	62	43.4	32.6	130.4 (100.8, 166)	-
Carolinian[a]	33	23.1	6.7	353.2 (247.2, 490.3)	-
Palauan	16	11.2	3.5	300.5 (177.9, 477.6)	1.8 (1.03, 3)
Chuukese	12	8.4	2.0	354.9 (192.3, 603.3)	2.13 (1.12, 3.77)
Filipino	8	5.6	25.5	18 (8.3, 34.1)	0.11 (0.05, 0.21)
Ponapean	5	3.5	1.1	281.3 (103.1, 623.5)	1.69 (0.61, 3.85)
Yapese	3	2.1	0.4	497.8 (126.6, 1355)	2.98 (0.75, 8.33)
Marshallese	2	1.4	0.4	418.5 (70.2, 1383)	2.51 (0.41, 8.47)
White American	1	0.7	1.7	31.2 (1.6, 153.8)	0.19 (0.01, 0.94)
Hawaiian	1	0.7	-	-	-
Other	0	0	25.1	0	0

[a] Indigenous population.
[b] Incidence rate ratios comparing combined indigenous Chamorro and Carolinian groups (167 per 100 000 person-years) to other ethnicities.

4. Discussion

In developing countries ARF and RHD are the leading causes of cardiovascular mortality during the first 50 years of life. Improved living standards are believed to account for the reduced rate of ARF in industrialized nations. Antimicrobial therapy of streptococcal pharyngitis and shifting serotypes have undoubtedly also contributed to the marked decrease in disease incidence. However, an unexplained, albeit geographically limited resurgence of ARF was recorded in the USA during the last two decades of the twentieth century.[8,9]

This investigation has produced the first incidence data of ARF for children in the Northern Mariana Islands. The average annualized incidence of ARF among all ethnic groups of 85.8 per 100 000 person-years for patients aged 5–14 years is comparable to other high incidence populations such as the New Zealand Maori and Pacific Islander populations.[10]

The indigenous populations of Chamorros and Carolinians constitute only 39.3% of the total population of the Northern Mariana Islands and have a combined average annualized incidence of 167 cases per 100 000 person-years. It appears that all Pacific Islander groups have a markedly higher incidence of ARF as compared to non-Pacific Island ethnic groups (Table 3). The reason for this increased incidence is unclear, but is consistent with previous findings among Samoans living in Hawaii.[3] While some of the represented ethnic groups had a small population during the study period, these findings are still quite provocative, and are an excellent area for further study.

In retrospect, the decision to exclude patient records that did not have the encounter for ARF diagnosis may have been too strict. As a consequence, our findings are biased to a lower incidence. It was not possible to calculate prevalence data for RHD as the record review included only outpatient visits for pediatric patients. While many patients are treated without a hospital admission for their ARF, those who were hospitalized during their initial attack of rheumatic fever and did not return to CHC for follow-up care were not identified. There are also patients with ARF who are treated in the private physician clinics; such patients may not have been identified through this chart review if they were receiving oral antibiotic secondary prophylaxis. Clearly this is a limitation of the study that leads to an underestimate of the incidence of ARF in the Northern Mariana Islands; a review of inpatient records would have provided more data. Those adults who were diagnosed prior to our study time period and are still living are another group not identified in the database query.

Only 75% of the patients in this review met strict Jones criteria based on the 1992 consensus report, however all had been diagnosed with ARF and referred for secondary antibiotic prophylaxis given the high incidence of disease in the community. Of the 25% of patients with incomplete diagnoses, most were diagnosed by multiple minor Jones criteria with evidence of streptococcal infection. Some charts, however, did not include throat culture or serology results, and these were considered incomplete diagnoses. Ralph et al. proposed an expansion of the diagnostic criteria in high incidence areas, and suggested the inclusion of 'probable' and 'possible' ARF to identify patients who may require secondary antibiotic prophylaxis and closer follow-up,[11] which is how this patient subset should have been treated. In addition, consideration should be given to the inclusion of monoarthritis as a major criterion in areas of high incidence.[12,13] It has been noted, however, that patients who present with monoarthritis may have been previously exposed to disease-altering NSAIDs before the diagnosis of ARF.[14] NSAID use prior to presentation could not be reliably extracted from the medical records in this study.

An antistreptolysin O titer of greater than 150 Todd units was considered evidence of prior streptococcal infection, although it has been suggested that in areas with higher background rates of streptococcal infections a higher cut-off should be used, even as high as 320 Todd units.[15] Using a cut-off of 320 Todd units, 29 patients would be eliminated from the data set because of no additional evidence of streptococcal infection. While there is certainly controversy regarding the reliability of the streptozyme assay, limited resources and availability of tests were considered when evaluating the data.

There has been an apparent increase in the annual incidence of ARF over time in the Northern Mariana Islands pediatric population (Table 2). Only seven cases were identified from 1984 through 1989, however few charts were reviewed from this time period, increasing the likelihood that additional diagnoses were missed. The data in Table 2 show a statistically significant increase in ARF incidence when comparing 2000–2006 to the three prior time periods. It is unclear at this time if the increase can be attributed to a true change in the number of cases, an increased awareness of ARF among patients and care providers, or improved detection after the acquisition of Doppler echocardiography equipment in 1999. Before 1999, 47% of patients presented with carditis and after 1999, 60% of patients presented with carditis. However, this only trended towards statistical significance and can be attributed to many factors other than the quality of echocardiography equipment. When available in the chart, only echocardiographic findings from the initial diagnostic evaluation were noted.

A recurrence rate of nearly 40% among our population is exceedingly high, despite a nurse-driven secondary prophylaxis program in both the pediatric and adult clinics at CHC. Also of note, was the high rate (31%) of positive group A streptococcal throat

cultures. Many patients are known to miss their bicillin doses or are lost to follow-up during the transition from pediatric to adult care, which occurs at 16 years of age in our facility. No centralized register of patients with ARF and RHD in the Northern Mariana Islands exists, although it is anticipated that the data reported here will facilitate its development to improve the administration of secondary prophylaxis.

The numerous patients found to have valvular thickening on echocardiogram at initial diagnosis suggests that there are patients who have prior or recurrent episodes of ARF that are undiagnosed. The factors that contribute to missed diagnoses are diverse and include lack of parental awareness of the potential seriousness of a child's complaint of pharyngitis and the lack of physician and nurse practitioner cognizance of the incidence of ARF in the Pacific Island populations, which may result in a less aggressive pursuit of ARF as a diagnosis.

The results of this study document the extremely high incidence of ARF in numerous ethnic groups of Pacific Island descent in the Northern Mariana Islands. Of note, Marijon et al. recently reported that the routine use of echocardiography to facilitate the diagnosis of ARF in Southeast Asian and sub-Saharan children resulted in a ten-fold higher prevalence of RHD than diagnosed by clinical examination alone.[16] Their data strongly support the assertion that ARF represents a much larger disease burden than previously thought and underscore the need for primary prevention of streptococcal infections and their long-term sequelae. Our data substantiate the need for increased and continued care provider education about ARF, its diagnosis and prevention, as well as secondary prophylaxis. Group A streptococcal vaccine trials have been initiated in North America. Characterization of the streptococcal isolates from Northern Mariana Islands patients with ARF will be vital to assure that appropriate vaccines are considered for Pacific Islander populations.

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